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Effect of Intravenous Ferric Carboxymaltose on Hemoglobin Response Among Patients With Acute Isovolemic Anemia Following Gastrectomy
The FAIRY Randomized Clinical Trial

Young-Woo Kim, PhD; Jae-Moon Bae, PhD; Young-Kyu Park, PhD; Han-Kwang Yang, PhD; Wansik Yu, PhD; Jeong Hwan Yook, PhD; Sung Hoon Noh, PhD; Mira Han, MS; Keun Won Ryu, PhD; Tae Sung Sohn, PhD; Hyuk-Joon Lee, PhD; Oh Kyoung Kwon, PhD; Seung Yeob Ryu, PhD; Jun-Ho Lee, PhD; Sung Kim, PhD; Hong Man Yoon, MD; Bang Wool Eom, PhD; Min-Gew Choi, PhD; Beom Su Kim, PhD; Oh Jeong, PhD; Yun-Suhk Suh, PhD; Moon-Won Yoo, PhD; In Seob Lee, PhD; Mi Ran Jung, PhD; Ji Yeong An, PhD; Hyoung-Il Kim, PhD; Youngsook Kim, BS; Hannah Yang, BS; Byung-Ho Nam, PhD; for the FAIRY Study Group

IMPORTANCE Acute isovolemic anemia occurs when blood loss is replaced with fluid. It is often observed after surgery and negatively influences short-term and long-term outcomes.

OBJECTIVE To evaluate the efficacy and safety of ferric carboxymaltose to treat acute isovolemic anemia following gastrectomy.

DESIGN, SETTING, AND PARTICIPANTS The FAIRY trial was a patient-blinded, randomized, phase 3, placebo-controlled, 12-week study conducted between February 4, 2013, and December 15, 2015, in 7 centers across the Republic of Korea. Patients with a serum hemoglobin level of 7 g/dL to less than 10 g/dL at 5 to 7 days following radical gastrectomy were included.

INTERVENTIONS Patients were randomized to receive a 1-time or 2-time injection of 500 mg or 1000 mg of ferric carboxymaltose according to body weight (ferric carboxymaltose group, 228 patients) or normal saline (placebo group, 226 patients).

MAIN OUTCOMES AND MEASURES The primary end point was the number of hemoglobin responders, defined as a hemoglobin increase of 2 g/dL or more from baseline, a hemoglobin level of 11 g/dL or more, or both at week 12. Secondary end points included changes in hemoglobin, ferritin, and transferrin saturation levels over time, percentage of patients requiring alternative anemia management (oral iron, transfusion, or both), and quality of life at weeks 3 and 12.

RESULTS Among 454 patients who were randomized (mean age, 61.1 years; women, 54.8%; mean baseline hemoglobin level, 9.1 g/dL), 96.3% completed the trial. At week 12, the number of hemoglobin responders was significantly greater for ferric carboxymaltose vs placebo. Compared with the placebo group, patients in the ferric carboxymaltose group experienced significantly greater improvements in serum ferritin level and transferrin saturation level; but there were no significant differences in quality of life. Patients in the ferric carboxymaltose group required less alternative anemia management than patients in the placebo group. The total rate of adverse events was higher in the ferric carboxymaltose group than the placebo group, but no severe adverse events were reported in either group.

Outcomes at Week 12	Ferric Carboxymaltose	Placebo	Absolute Difference (95% CI)	*P* Value
Hemoglobin responders, No. (%)	200 (92.2)	115 (54.0)	38.2 (33.6-42.8)	.001
Serum ferritin level, ng/mL	233.3	53.4	179.9 (150.2-209.5)	.001
Transferrin saturation level, %	35.0	19.3	15.7 (13.1-18.3)	.001
Alternative anemia management, %	1.4	6.9	5.5 (3.3-7.6)	.006
Adverse event rate, No. (%)	15 (6.8)	1 (0.4)		

CONCLUSION AND RELEVANCE Among adults with isovolemic anemia following radical gastrectomy, the use of ferric carboxymaltose compared with placebo was more likely to result in improved hemoglobin response at 12 weeks.

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Supplemental content

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Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The FAIRY Study Group members are listed at the end of this article.

Corresponding Author: Young-Woo Kim, MD, PhD, FRCS, Department of Cancer Control and Population Health, Graduate School of Cancer Science and Policy, 323 Ilsan-ro, Ilsandonggu, Goyang 10408, Republic of Korea (gskim@ncc.re.kr).

Perioperative anemia occurs in 25% to 75% of patients with cancer, and the prevalence of anemia in the immediate postoperative period after major surgery is as high as 90%.[1,2] Postoperative acute isovolemic anemia, which results from operation-related or trauma-related blood loss, can adversely affect recovery and quality of life (QOL) by subtly slowing reaction time, deteriorating memory, and decreasing energy levels.[3,4] Patients with gastric cancer who undergo gastrectomy are particularly affected by acute isovolemic anemia because of their decreased ability to absorb iron.[5] Some patients are unable to recover depleted iron stores and develop chronic anemia as a sequel to acute isovolemic anemia.[6] Moreover, a study found that anemia was the strongest prognostic factor for lower survival rates compared with those of patients with regular hemoglobin levels.[7]

Despite the high prevalence and poor outcome of anemia, blood management has been overlooked due to 2 main reasons. First, oral iron supplementation immediately after gastrectomy can aggravate gastrointestinal dysfunction, leading to the decision to wait for spontaneous recovery. Second, the controversial practice of blood transfusion is widespread and frequently part of the standard of care for patients with anemia,[3,8] despite its demonstrated inability to replenish iron stores[9] and emerging status as an independent risk factor for complications and poor survival outcomes.[10,11]

A previous retrospective study suggested that a greater proportion of patients treated with ferric carboxymaltose, a dextran-free intravenous iron complex, experienced an effective reversal of acute isovolemic anemia compared with no treatment.[6] Compared with oral iron, a high-dose infusion of iron is also associated with faster and higher replenishment of depleted hemoglobin and iron levels and is not associated with serious gastrointestinal adverse events.[12] To our knowledge, however, no randomized trials have confirmed this observation.

The Ferric Carboxymaltose for Acute Isovolemic Anemia Following Gastrectomy (FAIRY) randomized clinical trial was therefore designed to evaluate the efficacy of intravenous ferric carboxymaltose for the treatment of acute isovolemic anemia following gastrectomy for gastric cancer.

Key Points

Question Does administration of ferric carboxymaltose effectively improve hemoglobin response in patients presenting with acute isovolemic anemia following gastrectomy?

Findings In this randomized clinical trial of 454 adults, the use of ferric carboxymaltose compared with placebo was significantly more likely to result in an effective hemoglobin response (92.2% vs 54.0%).

Meaning In patients presenting with acute isovolemic anemia after gastrectomy, administration of ferric carboxymaltose may improve hemoglobin response.

Methods

Study Design

This was a multicenter, randomized, patient-blinded, placebo-controlled, phase 3 study conducted at 7 major institutions in the Republic of Korea. The study design has been published previously,[13] and the protocol was approved by the institutional review board of the National Cancer Center, Korea, on November 7, 2012 (NCCCTS-12-644) (Supplement 1). The statistical analysis plan is available in Supplement 2. Each participating center obtained committee approval. The National Cancer Center was responsible for on-site monitoring of the study locations to verify the accuracy of the acquired data and examine whether the study protocol followed regulations. Signed consent forms were obtained from all participants.

The study was conducted in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice guidelines, and local and national regulations. An independent data and safety monitoring board reviewed the safety data.

Patients

Patients 20 years or older with acute isovolemic anemia (hemoglobin level, ≥7-<10 g/dL) at 5 to 7 days after gastrectomy for gastric cancer were eligible for this study. The indicated hemoglobin range was used to assess for moderate anemia.[14] Guidelines indicate a need for transfusion if hemoglobin levels fall below 7 g/dL.[15] Levels more than 10 g/dL to 12 g/dL or 13 g/dL indicate mild anemia, which does not justify the use of intravenous iron. Patients were excluded from the study if they had the following: concurrent medical condition(s) that would prevent adherence or jeopardize their health; hypersensitivity to any component of the formulation; active severe infection or inflammation; receipt of transfusion, erythropoietin-stimulating agent, or more than 500 mg of intravenous iron within 4 weeks prior to screening; history of acquired iron overload, pregnancy or lactation, decreased renal function (defined as creatinine clearance of <50 mL/min calculated according to Cockcroft-Gault [to convert creatinine to μmol/L, multiply by 88.4]); chronic liver disease or increase in liver enzymes (alanine and aspartate aminotransferase) more than 3 times the upper limit of the normal range; American Society of Anesthesiology score of more than 3, Eastern Cooperative Oncology Group performance status score of more than 1; or participation in any other interventional study within 1 month prior to screening.

Randomization and Masking

Patients were stratified at each study site during randomization based on their clinical stage of gastric cancer (according to the American Joint Commission on Cancer tumor-node-metastasis [TNM] system): stage I (does not require adjuvant chemotherapy after gastrectomy) and stages II through IV (requires adjuvant or palliative chemotherapy after gastrectomy). Group allocation was randomly assigned (1:1) by a data management system (Velos eResearch, Velos). A random permutation method with block sizes 2, 4, and 6 were used. The randomized patients were blinded to their group allocation to minimize reporting bias for the QOL assessments. The intravenous line was covered with black vinyl to ensure patient blinding, and the placebo was administered over the equivalent

period. The care of patients was standardized between the 2 groups, apart from the delivered treatment. All patients were informed about the trial by the study investigator or an authorized associate.

Procedures

The experimental group received ferric carboxymaltose (1000 mg for a body weight of ≥50 kg or 500 mg for a body weight of <50 kg), and the placebo group received normal saline (0.9% sodium chloride solution; 200 mL for a body weight of ≥50 kg or 100 mL for a body weight of <50 kg). The 2 categorized dosages were based on manufacturer's instructions and a previous trial indicating its support of fixed, weight-based dosing compared with the Ganzoni-calculated regimen.[16] Patients with a serum ferritin level of less than 15 ng/mL (to convert ferritin to pmol/Lng/mL, multiply by 2.247) and a hemoglobin level less than 10 g/dL received an additional dose of 500 mg of ferric carboxymaltose or 100 mL of normal saline (placebo) at week 3. Ferric carboxymaltose was administered as a single intravenous drip infusion mixed with 100 mL or 200 mL of normal saline or an undiluted bolus injection with an administration time of 15 minutes for 1000 mg or 6 minutes for 500 mg.

Outcomes

The primary efficacy end point was the number of hemoglobin responders by week 12. Hemoglobin responders were defined as patients who achieved an increase in hemoglobin levels of 2 g/dL or more[14] from baseline to week 12, hemoglobin levels of 11 g/dL or more at week 12, or both.[16] Secondary efficacy end points were the percentage of patients with hemoglobin levels of 10 g/dL or more, 11 g/dL, and 12 g/dL by weeks 3 and 12, the percentage of patients requiring alternative anemia management therapy, self-reported QOL assessments at weeks 3 and 12, and changes in hemoglobin, ferritin, and transferrin saturation (TSAT) levels over the study duration.

QOL was assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30), version 3.0, and the gastric cancer–specific module QLQ-STO22[17] at baseline and weeks 3 and 12. The EORTC QLQ-C30 is a brief, validated, self-reporting, cancer-specific measure of QOL comprised of the following: multiple scales that evaluate physical, role, emotional, cognitive, and social functioning; 1 global health status/QOL scale; 3 symptom scales measuring fatigue, pain, and nausea or vomiting; 6 single units assessing other symptoms (dyspnea, insomnia, appetite loss, constipation, and diarrhea); and financial difficulties. The EORTC QLQ-STO22 is a 22-item questionnaire that incorporates 5 multi-item scales (dysphagia, pain, reflux, eating, and anxiety) and 4 questions covering disease, treatment-related symptoms, and specific emotional consequences of gastric cancer. The QLQ-C30 and QLQ-STO22 questionnaires were scored according to the EORTC scoring manual and converted to a scale of 0 to 100; higher scores indicated healthier functioning for functional scales or worsening symptomatology for symptom scales. A 10-point difference in the mean score was accepted as a minimal clinically important difference in health-related QOL.

Safety and tolerability were monitored throughout the study. Stopping rules of the study medication did not apply owing to the single administration of ferric carboxymaltose. In the potential case of hypersensitivity or anaphylactic reactions, immediate interruption of infusion was mandatory. Further management was left to the discretion of the physician on duty.

Post hoc, exploratory subgroup analyses of hemoglobin responders were performed according to various clinicopathological factors relevant to changes in hemoglobin: chemotherapy required or not required, type of operation, serum ferritin level less than 30 ng/mL or 30 ng/mL or more, and TSAT less than 20% or 20% or more at week 12.

Statistical Analysis

The sample size was calculated based on a superiority design assuming ferric carboxymaltose response (according to primary end point definition) of 75% by week 12 and a response of 60% in the placebo group by week 12. The expected rate of improvement for patients in the ferric carboxymaltose group is at least 15% higher (ie, 75% hemoglobin responders) compared with the placebo group. We used 15% as a minimal clinically important difference due to a published document submitted for approval of ferric carboxymaltose by the US Food and Drug Administration (FDA).[18] Using these estimates, 400 patients were required to detect a significant difference at the 5% level with 90% power:

$$n = f(\alpha, \beta) \times [p1 \times (100 - p1) + p2 \times (100 - p2)]/(p2 - p1)^2$$

where p1 and p2 are the percentage "success" in the placebo group (p1) and ferric carboxymaltose group (p2) and $f(\alpha, \beta) = [\Phi^{-1}(\alpha/2) + \Phi^{-1}(\beta)]$.[2]

To account for potential patient dropouts, the sample size was estimated at 450 patients (225 per group). The number of missing data was small (0.7% at week 3 and 1.8% at week 12) and therefore excluded from analysis.[19] Modified intention-to-treat analysis, which excluded missing cases, was performed with the full analysis set, which involved patients who had results of at least 1 postbaseline hemoglobin measurement among the safety set.

Baseline characteristics and iron parameters were analyzed using the Pearson χ^2 test or 2-tailed Fisher exact test (patients' age and sex, clinicopathological data, and morbidity) and a *t* test (hemoglobin level before treatment and hospital days after treatment). The *z* score test was used to determine whether a significant difference existed between the 2 groups with respect to the changes in hemoglobin level during follow-up. Odds ratios (ORs) were derived from univariable analysis because baseline variables were well matched, with the exception of hemoglobin. Post hoc multivariable Cox proportional hazard was implemented to adjust for difference in baseline hemoglobin values.

The linear mixed model was used to calculate the QOL differences between the groups over time.[18] Baseline scores and the interaction between time and group were also included in the linear mixed model. Covariables such as sex and age of patients were not included in the model as there were no differences between the 2 groups.

A post hoc *t* test was performed to compare effects of ferric carboxymaltose vs placebo on hospital length of stay, and

linear mixed-effects modeling was performed with site and stage as the random factors. χ^2 and Fisher exact tests were performed for subgroup analyses. Post hoc χ^2 test was used to compare differences in patients who received preoperative oral iron with 4 weeks of surgery and those who did not. Rank sum tests were conducted to evaluate variable distribution due to skewing of data. All tests were 2-sided with a *P* value of less than .05 for significance (MIXED procedure of the SAS program [SAS Institute], version 14).

Results

Patient Disposition

Recruitment began on February 4, 2013, and continued through September 21, 2015. A total of 454 patients were enrolled and randomized to receive ferric carboxymaltose (228 patients) or placebo (226 patients). Only 445 patients (ferric carboxymaltose, 222; placebo, 223) were included in the safety analysis set and 437 in the full analysis set (ferric carboxymaltose, 218 patients; placebo, 219 patients) (**Figure 1**). At baseline, the mean age of all patients was 61.1 years, and the mean serum hemoglobin level was 9 g/dL for the ferric carboxymaltose group and 9.2 g/dL for the placebo group (*P* = .01). The mean estimated blood loss was 187 mL (SD, 175) in the ferric carboxymaltose group and 192 mL (SD, 167) in the placebo group (*P* = .72) (**Table 1**).

Primary End Point

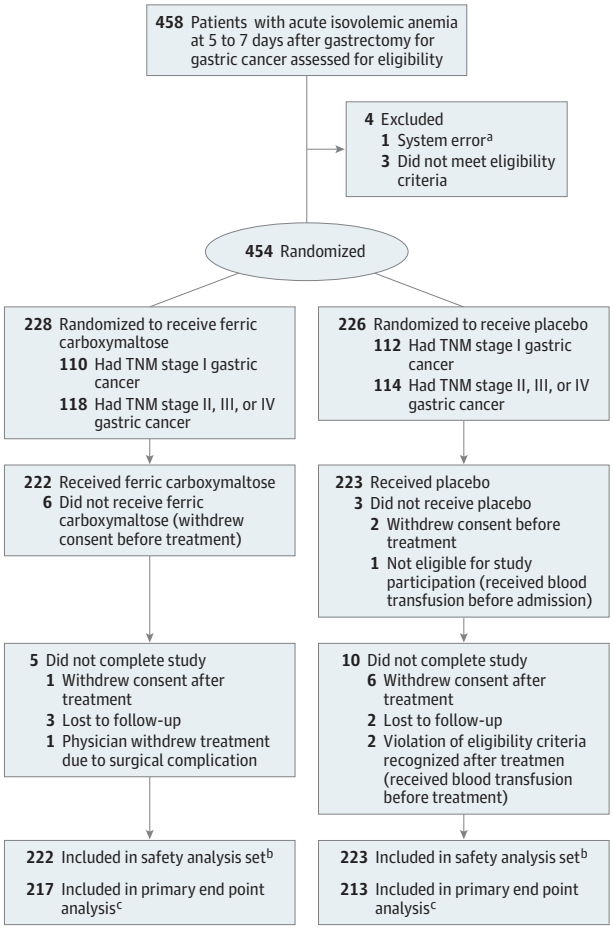
Among 437 patients of the full analysis set population, the primary end point was ascertained for 430 patients with a hemoglobin measurement at week 12 (ferric carboxymaltose group, 217 patients; placebo group, 213 patients; Figure 1). The number of hemoglobin responders at week 12 was significantly greater in the ferric carboxymaltose group compared with the placebo group (92.2% [200 patients] in the ferric carboxymaltose group vs 54.0% [115 patients] in the placebo group; absolute difference, 38.2% [95% CI, 33.6% to 42.8%]; *P* = .001) (**Table 2**).

Secondary Efficacy End Points

For the secondary analyses, including the QOL measures, there was no adjustment for multiple comparisons; accordingly, these findings should be considered exploratory. The proportion of patients who achieved anemia correction and improved iron parameters all significantly favored ferric carboxymaltose at all time points (eTable 1 in Supplement 3). Compared with the placebo group, a significantly greater proportion of patients in the ferric carboxymaltose group obtained hemoglobin levels of 10 g/dL or more, 11 g/dL, and 12 g/dL at week 3 (≥10 g/dL: 96.8% in the ferric carboxymaltose group vs 71.1% in the placebo group; absolute difference, 25.7% [95% CI, 21.6%-29.8%], *P* = .001; 11 g/dL: 76.0% in the ferric carboxymaltose group vs 41.3% in the placebo group; absolute difference, 34.7% [95% CI, 30.3%-39.2%], *P* = .001; 12 g/dL: 35.5% in the ferric carboxymaltose group vs 12.4% in the placebo group; absolute difference, 23.1% [95% CI, 19.1%-27.1%], *P* = .001) and week 12 (≥10 g/dL: 97.2% in the ferric carboxymaltose group vs 72.3% in the placebo group; absolute difference, 24.9% [95% CI, 20.8%-29.0%], *P* = .001; 11 g/dL: 88.0% in the ferric carboxymaltose group vs 46.9% in the placebo group; absolute difference, 41.1% [95% CI, 36.4%-45.7%], *P* = .001; 12 g/dL: 63.6% in the ferric carboxymaltose group vs 23.0% in the placebo group; absolute difference, 40.6% [95% CI, 35.9%-45.2%], *P* = .001). The difference was more than 20% at all time points, and a nearly 3-fold increase—the greatest difference achieved—was recorded at week 12 for hemoglobin level of 12 g/dL or more (eTable 1 in Supplement 3).

Significantly more patients in the placebo group required alternative anemia management therapy compared with patients treated with ferric carboxymaltose (1.4% in the ferric carboxymaltose group vs 6.8% in the placebo group; absolute difference, 5.5%, [95% CI, 3.3%-7.6%], *P* = .006). eTable 2 in

Figure 1. Flow of Patients Through the Study of Ferric Carboxymaltose for Postgastrectomy Anemia



TNM indicates tumor-node-metastasis.

[a] One systemwide test run conducted prior to randomization of first patient to ensure functional capacity of the eVelos system.

[b] Safety analysis set included patients who received ferric carboxymaltose or placebo after randomization.

[c] At week 12, five patients in the ferric carboxymaltose group lacked a postbaseline hemoglobin measurement; 10 patients in the placebo group lacked a postbaseline hemoglobin measurement.

Table 1. Baseline Characteristics for Patients With Acute Isovolemic Anemia Following Gastrectomy Receiving Ferric Carboxymaltose vs Placebo

Characteristics	No. (%) Total (N = 454)	Ferric Carboxymaltose (n = 228)	Placebo, (n = 226)
Age, mean (SD), y	61.1 (13.1)	60.9 (13.7)	61.2 (12.6)
Sex			
Male	205 (45.2)	103 (45.2)	102 (45.1)
Female	249 (54.8)	125 (54.8)	124 (54.9)
Body weight, mean (SD), kg	57.8 (9.8)	57.6 (9.7)	58.1 (9.9)
Comorbidities			
Diabetes	83 (29.7)	39 (29.5)	44 (29.9)
Hypertension	164 (58.8)	74 (56.1)	90 (61.2)
Tuberculosis	31 (11.1)	19 (14.4)	12 (8.2)
Chronic liver disease	1 (0.4)	0	1 (0.7)
Hematologic Values, Mean (SD)[a]			
Preoperative hemoglobin, g/dL	11.7 (1.6)	11.6 (1.6)	11.8 (1.6)
Hemoglobin at enrollment, g/dL	9.1 (0.7)	9.0 (0.7)	9.2 (0.7)
Serum ferritin, ng/mL	126.5 (115.1)	115.9 (104.8)	137.1 (123.9)
Iron, µg/dL	24.3 (13.3)	24.6 (15.2)	24.0 (11.1)
Total iron-binding capacity, µg/dL	242.1 (57.2)	243.6 (56.2)	240.6 (58.2)
Transferrin saturation, %	10.7 (6.4)	10.8 (7.2)	10.5 (5.4)
Creatinine clearance rate, mg/dL	91.3 (33.6)	91.2 (33.4)	91.4 (33.8)
C-reactive protein, median (Q1-Q3), mg/dL	4.7 (2.6-7.8)	4.3 (2.5-7.1)	5.4 (2.8-8.2)
Surgical Operation Characteristics			
Gastrectomy			
Total	167 (36.8)	87 (38.2)	80 (35.4)
Partial	287 (63.2)	141 (61.8)	146 (64.6)
Surgical approach			
Open gastrectomy	336 (74.0)	171 (75.0)	165 (73.0)
Laparoscopy or robot-assisted gastrectomy	118 (26.0)	57 (25.0)	61 (27.0)
Estimated blood loss, mean (SD), mL	188.1 (171.4)	186.5 (175.5)	191.5 (167.2)
Intraoperative complications			
Bleeding	15 (75.0)	9 (75.0)	6 (75.0)
Other organ injury	4 (20.0)	2 (16.7)	2 (25.0)
Open conversion from laparoscopic surgery	1 (5.0)	1 (8.3)	0
Gastric Cancer Characteristics			
TNM stage			
I[b]	222 (48.9)	110 (48.3)	112 (49.6)
II, III, or IV	232 (51.1)	118 (51.7)	114 (50.4)
Chemotherapy			
None	273 (60.1)	136 (59.6)	137 (60.6)
Adjuvant	174 (38.3)	86 (37.7)	88 (38.9)
Palliative	7 (1.6)	6 (2.6)	1 (0.5)

Abbreviation: TNM, tumor-node-metastasis.

SI conversion factors: To convert C-reactive protein to nmol/L, multiply by 9.524; creatinine to µmol/L, multiply by 88.4; ferritin to pmol/Lng/mL, multiply by 2.247; iron and iron-binding capacity to µmol/L, multiply by 0.179.

[a] Baseline hematologic values were measured in all randomized patients between 5 to 7 days following gastrectomy (mean [SD]), except preoperative hemoglobin.

[b] Clinical gastric tumor staging according to the American Joint Commission on Cancer TNM system.

Supplement 3 describes the use of alternative anemia management therapy (oral iron, transfusion, or both) in the primary analysis population. No patients received erythropoiesis-stimulating agents.

At week 3, the increase in hemoglobin levels was significantly greater in the ferric carboxymaltose group (2.6 g/dL) than the placebo group (1.4 g/dL; $P < .001$); and by week 12, the increase in hemoglobin levels was faster in patients treated with ferric carboxymaltose (3.3 g/dL) than patients treated with placebo (1.6 g/dL; $P < .001$) (**Figure 2**).

At weeks 3 and 12, significant changes in serum ferritin levels were observed between the ferric carboxymaltose and placebo groups. Compared with baseline, mean serum ferritin levels increased in the ferric carboxymaltose group, but decreased in the placebo group (week 3: 508.8 ng/mL in the ferric carboxymaltose group vs 75.6 ng/mL in the placebo group; absolute difference, 433.2 ng/mL [95% CI, 381.18-485.25], $P = .001$; week 12: 233.3 ng/mL in the ferric carboxymaltose group vs 53.4 ng/mL in the placebo group; absolute difference, 179.9 ng/mL [95% CI, 150.2-209.5], $P = .001$).

Table 2. Primary Analysis of Patients With Acute Isovolemic Anemia Following Gastrectomy Receiving Ferric Carboxymaltose vs Placebo By Week 12

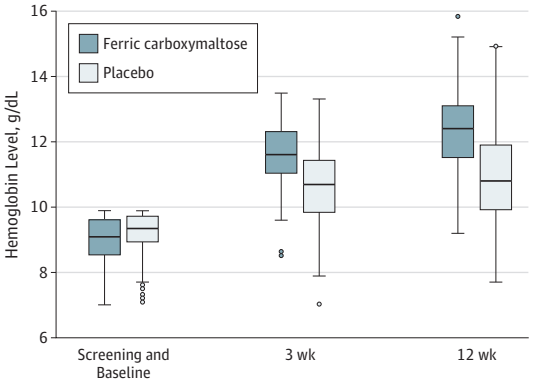
	Total Patients in Primary Analysis, No. (%) (N = 430)[a]	Hb Responders, No. (%)[b]		Absolute Difference, % (95% CI)
		Ferric Carboxymaltose (n = 217)	Placebo (n = 213)	
Hb increase of ≥2 g/dL from baseline, Hb level of ≥11 g/dL, or both (primary outcome)	315 (73.3)	200 (92.2)	115 (54.0)	38.20 (33.6-42.8)
Hb increase of ≥2 g/dL from baseline	277 (64.4)	191 (88.0)	86 (40.4)	47.60 (42.9-52.4)
Hb level of ≥11 g/dL	291 (67.7)	191 (88.0)	100 (46.0)	41.10 (36.4-45.7)

Abbreviation: Hb, hemoglobin.

[a] No. of patients with an Hb measurement at 12 weeks.

[b] Hb responder was defined as a hemoglobin increase of 2 g/dL or more from baseline, a hemoglobin level of 11 g/dL or more, or both at week 12.

Figure 2. Hemoglobin Levels Among Patients Receiving Ferric Carboxymaltose vs Placebo Over Time



No. of participants			
Ferric carboxymaltose	228	217	217
Placebo	226	218	213

The solid line in each box indicates the median. The top line of the box indicates the 75th percentile, and the bottom line of the box indicates the 25th percentile. The top and bottom whiskers indicate the upper and lower adjacent values, respectively. The circles represent the outlier values.

Significant changes were also observed in transferrin saturation levels (week 3: 29.8% in the ferric carboxymaltose group vs 13.9% in the placebo group; absolute difference, 15.9% [95% CI, 14.1%-17.7%], $P = .001$; week 12: 35.0% in the ferric carboxymaltose group vs 19.3% in the placebo group; absolute difference, 15.7% [95% CI, 13.1%-18.3%], $P = .001$).

QOL Assessments With EORTC QLQ-C30 and QLQ-STO22

The overall proportion of completed QOL assessments was greater than 95% at all time points (96.9% at week 3; 95.4% at week 12). No significant difference was observed in the global health status/QOL scale at weeks 3 and 12. The predefined 10-point minimal clinical difference was not met, and therefore no clinical significance was observed (eTable 3 in Supplement 3).

Safety and Tolerability of Ferric Carboxymaltose

The total rate of adverse events was higher in the ferric carboxymaltose group than the placebo group (ferric carboxymaltose group, 15 patients [6.8%]; placebo group, 1 patient [0.4%]). Ferric carboxymaltose-related adverse events included injection site reactions in 5 patients (2.3%) and urticaria in 5 patients (2.3%); all other adverse events were reported in 1 patient in each group (0.5%) (eTable 3 in Supplement 3). All adverse events were reported as a grade 1 severity except injection site reactions and urticaria, which were reported as grades 1 and 2. Other reported study drug-related adverse events included constipation, fever, headache, insomnia, and phlebitis. Otherwise, ferric carboxymaltose was well tolerated with no serious adverse events, such as hypersensitivity or anaphylactic reactions (eTable 4 in Supplement 3). No patients received an undiluted bolus injection, and 1 patient received an additional dose of ferric carboxymaltose at week 3.

Post Hoc Analysis

Hemoglobin response was significantly greater in the ferric carboxymaltose group compared with the placebo group in all exploratory subgroups (eFigure 2 in the Supplement). Analysis comparing the effects of ferric carboxymaltose vs placebo on mean hospital length of stay was not statistically significant (ferric carboxymaltose group, 10.7 days [SD, 7.9]; placebo group, 10.9 days [SD, 13.8]; difference, 0.2 days [95% CI, −2.341 to 1.789], $P = .79$). Analysis of hemoglobin response in patients who received preoperative oral iron within 4 weeks before enrollment compared with those who did not was not statistically significant (2.4% of randomized patients; 4 of 4 patients in the ferric carboxymaltose group and 3 of 7 patients in the placebo group; $P = .47$); therefore, preoperative oral iron was not associated with measured end points as a confounder. After adjusting for potentially significant baseline differences, multivariable analysis showed that the ferric carboxymaltose group experienced a significantly greater proportion of hemoglobin responders compared with the placebo group (OR, 12.08 [95% CI, 6.70 to 21.78]; $P < .001$) (eTable 5 in Supplement 3). Results of the linear mixed model were similar to results from analysis of the primary end point (OR, 10.10 [95% CI 5.73 to 17.81]; $P < .001$).

Discussion

In this randomized clinical trial of patients with isovolemic anemia following gastrectomy, a 1-time or 2-time infusion of either 500 mg or 1000 mg of ferric carboxymaltose compared with placebo significantly increased serum hemoglobin levels in 92.2% patients in the ferric carboxymaltose

group vs 54.0% of patients in the placebo group (P = .001). The results of the secondary end points were consistent with the primary end point and demonstrated increased hemoglobin and iron levels over time, decreased need for alternative treatments for anemia. The benefits of this short and easily administered therapy were immediate and sustained as measured through increased hemoglobin and iron levels over time and a decreased need for alternative treatments for anemia. Overall, there was no clinically significant difference in QOL at weeks 3 and 12. Post hoc analysis showed improved hemoglobin response to ferric carboxymaltose in all exploratory subgroups.

Treatment with ferric carboxymaltose was also associated with minimal toxicity and was well tolerated. To date, more than 3600 patients have been treated with ferric carboxymaltose in various clinical trials, and the replenishment of iron stores with minimal adverse effects has been consistently reported.[12,20] In a previous study that evaluated the safety profile of a pooled database of 5799 patients exposed to 750 mg of ferric carboxymaltose, only low-grade and transient adverse events were reported in at least 1% of patients who were treated.[18] Commonly reported adverse events included injection-site reactions, nausea, constipation, headache, and diarrhea. Similar to this study, all adverse events were mild to moderate in severity (grade 1 or 2) with no grade 3 or 4 reactions.

QOL measurements over time showed ferric carboxymaltose–related improvements in fatigue and dyspnea but did not meet the predefined clinically relevant QOL improvement criterion. This may be because the patients were enrolled into this study immediately after receiving a major surgery, and there may be confounding factors influencing QOL that could not be distinguished by the questionnaires.

Limitations

This study has several limitations. First, the results of the secondary analyses and post hoc subgroup analysis were exploratory in nature and should be viewed as hypotheses. Further studies are needed to confirm these findings. Second, the effect of ferric carboxymaltose on long-term survival is considered hypothesis-generating, and there may be hidden complications that have not yet been determined.[21] Future studies should be directed toward analyzing the long-term effects of ferric carboxymaltose.

Conclusion

Among adults with isovolemic anemia following radical gastrectomy, the use of ferric carboxymaltose compared with placebo was more likely to result in improved hemoglobin response at 12 weeks.

ARTICLE INFORMATION

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Author Affiliations: Department of Cancer Control and Population Health, Graduate School of Cancer Science and Policy, National Cancer Center, Goyang, Republic of Korea (Y.-W. Kim); Center for Gastric Cancer, Research Institute and Hospital, National Cancer Center, Goyang, Republic of Korea (Y.-W. Kim, K. W. Ryu, Yoon, Eom, Y. Kim, H. Yang); Center for Gastric Cancer, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea (Bae, Sohn, J.-H. Lee, S. Kim, Choi, An); Department of Gastroenterologic Surgery, Chonnam National University Hwasun Hospital, Hwasun County, Republic of Korea (Park, S. Y. Ryu, Jeong, Jung); Department of Surgery, Seoul National University College of Medicine, Seoul, Republic of Korea (H.-K. Yang, H.-J. Lee, Suh); Center for Gastric Cancer, Gastric Cancer Center, Kyungpook National University Medical Center, Daegu, Republic of Korea (Yu, Kwon); Center for Gastric Cancer, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea (Yook, B. S. Kim, Yoo, I. S. Lee); Department of Gastrointestinal Surgery, Yonsei University Health System, Seoul, Republic of Korea (Noh, H.-I. Kim); Cancer Registration and Biostatistics Branch, Center for Clinical Trials, National Cancer Center, Goyang, Republic of Korea (Han, Nam).

Author Contributions: Dr Y.-W. Kim had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Y-W Kim and Bae contributed equally as primary authors.
Concept and design: Y.-W. Kim, Bae, Park, H.-K. Yang, Yu, Yook, Noh, Y. Kim, Nam.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: Y.-W. Kim, Bae, Yu, Han, H. Yang, Y. Kim, Nam.
Statistical analysis: Y.-W. Kim, Han, Y. Kim, Nam.
Obtained funding: Y.-W. Kim.
Administrative, technical, or material support: Y.-W. Kim, Bae, Park, H.-K. Yang, Yu, Yook, Noh, Y. Kim, Nam.
Supervision: Y.-W. Kim, Bae, Park, H.-K. Yang, Yu, Yook, Noh, Y. Kim, Nam.
Manuscript revisions: Y.-W. Kim, Y. Kim, H. Yang.

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Group Information: The FAIRY Study Group members are Young-Woo Kim (principal investigator [PI] and secretary general); Wansik Yu, Sung Hoon Noh, Han-Kwang Yang, Jae-Moon Bae, Young-Kyu Park, and Jeong Hwan Yook (all site PIs); Sung Kim, Tae Sung Sohn, Keun Won Ryu, Seung Yeob Ryu, Jun-Ho Lee, Oh Kyoung Kwon, Hyuk-Joon Lee, Min-Gew Choi, Oh Jeong, Ji Yeong An, Hong Man Yoon, Hyoung-Il Kim, Bang Wool Eom, Moon-Won Yoo, Beom Su Kim, Yun-Suhk Suh, In Seob Lee, and Mi Ran Jung(all investigators); and Byung-Ho Nam (principal biostatistician).

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